Sustainable responses in metastatic melanoma patients with and without brain metastases after elective discontinuation of anti-PD1-based immunotherapy due to complete response

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Abstract: BACKGROUND Anti-PD1-based immunotherapy is currently used in most patients with advanced melanoma. Despite the remarkable data regarding overall survival, the optimal treatment duration is still unknown. METHODS We evaluated the outcome of 125 patients with advanced melanoma with and without brain metastases (MBM), treated either with anti-PD1 monotherapy (N = 97) or combined with anti-CTLA4 (N = 28) after elective treatment discontinuation due to complete response (CR) (group A, N = 86), or treatment-limiting toxicity (N = 33) and investigator's decision (ID, N = 6) (group B) with subsequent CR. RESULTS For group A, median duration of treatment (mDoT) was 22 months (range 5-49) and median time to CR 9 months (range 2-47). Accordingly, mDoT for group B was 3 months (range 0-36) and median time to CR 7 months (range 1-32). Seven patients from group A and three from group B experienced disease recurrence. Off-treatment survival was not reached. Median off-treatment response time (mOTRt) was 19 months (range 0-42) and 25 months (range 0-66), respectively. For MBM, mOTRt was 17 months (range 7-41) and 28 months (range 9-39), respectively. After a median follow-up of 38 months (range 9-70), seven (5.6%) patients had deceased, one (0.8%) due to melanoma. CONCLUSIONS Treatment discontinuation is feasible also in patients with MBM. Efficacy outcomes seemed to be similar in both groups of patients who achieved CR, regardless of reason for discontinuation. In patients who experienced disease relapse, treatment re-challenge with anti-PD1 resulted in subsequent renewed response.

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Original Research

Sustainable responses in metastatic melanoma patients with and without brain metastases after elective discontinuation of anti-PD1-based immunotherapy due to complete response

Florentia Dimitriou [a], Anne Zaremba [b], Clara Allayous [c], Katharina C. Kähler [d], Camille L. Gerard [e], Lucia Festino [f], Sarah Schäfer [g], Frédéric Toussaint [h], Lucie Heinzerling [h], Jessica C. Hassel [g], Paolo A. Ascierto [f], Olivier Michielin [e], Axel Hauschild [d], Céleste Lebbe [c], Elisabeth Livingstone [b], Egle Ramelyte [a], Phil F. Cheng [a], Reinhard Dummer [a,*,1], Joanna Mangana [a,1]

[a] *Department of Dermatology, University Hospital Zurich, Zurich, Switzerland*
[b] *Department of Dermatology, University Hospital Essen, Essen, Germany*
[c] *APHP Department of Dermatology, Paris University Saint-Louis Hospital, U976, Paris, France*
[d] *Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Germany*
[e] *Precision Oncology Center, Department of Oncology, Lausanne University Hospital CHUV, Lausanne, Switzerland*
[f] *Melanoma Unit, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy*
[g] *Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany*
[h] *Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Germany*

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Abbreviations: CR, complete response; CTCAE v4, Common Terminology Criteria for Adverse Events version 4; CTLA-4, cytotoxic T-lymphocyte-associated Protein 4; DoR, duration of response; EOT, end of treatment; ICIs, immune checkpoint inhibitors; ID, investigator's decision; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; MBM, melanoma brain metastases; mDoT, median duration of response; mFU, median follow-up; OP, operation; OS, overall survival; OTRt, off-treatment response time; OTS, off-treatment survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; RR, response rate; SD, stable disease; SRT, stereotactic radiotherapy; TLT, treatment-limiting toxicity.

* *Corresponding author*: Department of Dermatology, University Hospital of Zurich, Gloriastrasse 31, Zurich, 8091, Switzerland. Fax: +0041 (44) 255 3999.
E-mail address: reinhard.dummer@usz.ch (R. Dummer).
[1] Equally contributed as Joint Last Authors.

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KEYWORDS
Melanoma;
Anti-PD1 treatment;
Immunotherapy;
Discontinuation;
Brain metastases

Abstract ***Background:*** Anti-PD1–based immunotherapy is currently used in most patients with advanced melanoma. Despite the remarkable data regarding overall survival, the optimal treatment duration is still unknown.
Methods: We evaluated the outcome of 125 patients with advanced melanoma with and without brain metastases (MBM), treated either with anti-PD1 monotherapy (N = 97) or combined with anti-CTLA4 (N = 28) after elective treatment discontinuation due to complete response (CR) (**group A**, N = 86), or treatment-limiting toxicity (N = 33) and investigator's decision (ID, N = 6) (**group B**) with subsequent CR.
Results: For **group A**, median duration of treatment (mDoT) was 22 months (range 5–49) and median time to CR 9 months (range 2–47). Accordingly, mDoT for **group B** was 3 months (range 0–36) and median time to CR 7 months (range 1–32). Seven patients from **group A** and three from **group B** experienced disease recurrence. Off-treatment survival was not reached. Median off-treatment response time (mOTRt) was 19 months (range 0–42) and 25 months (range 0–66), respectively. For MBM, mOTRt was 17 months (range 7–41) and 28 months (range 9–39), respectively. After a median follow-up of 38 months (range 9–70), seven (5.6%) patients had deceased, one (0.8%) due to melanoma.
Conclusions: Treatment discontinuation is feasible also in patients with MBM. Efficacy outcomes seemed to be similar in both groups of patients who achieved CR, regardless of reason for discontinuation. In patients who experienced disease relapse, treatment re-challenge with anti-PD1 resulted in subsequent renewed response.

1. Introduction

The application of antibody-mediated blockade of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4; ipilimumab) and programmed cell-death protein 1 (PD-1; pembrolizumab and nivolumab) immune checkpoint inhibitors (ICIs) in the treatment of advanced melanoma highly improved patient outcomes [1–4]. The durability of responses and improved overall survival (OS) has led to the widespread use of these immunotherapeutic agents as first-line treatment in most patients regardless of mutational status [1].

First evaluated in the KEYNOTE-001 study, pembrolizumab provided a response rate (RR) of 34% and median OS of 25.9 months with sustainable responses even after treatment discontinuation [5]. Combination therapy with concurrent use of nivolumab and ipilimumab has shown even higher efficacy, with an RR of 57.6% [6]. Updated results from phase III clinical trials show a sustained clinical benefit in both monotherapy and combinational treatment, regardless of *BRAF* mutational status [7,8]. It is also significant that 19% of the patients treated with anti-PD1 monotherapy and 22% with ipilimumab/nivolumab achieve a complete response (CR), which seems to be durable even after treatment cessation. Notably, subgroup analysis from randomized clinical trials indicate that progression-free survival (PFS) rates in patients with CR who discontinue pembrolizumab after at least 6 months are similar to those who complete 2 years of treatment as per the study protocol [4,9]. Despite these remarkable data on OS, the optimal treatment duration is still questionable.

In this retrospective multicenter study, we evaluated the outcome of advanced melanoma patients treated with anti-PD1–based immunotherapy after discontinuation of systemic therapy due to CR, or treatment-limiting toxicity (TLT) and investigator's decision (ID), with subsequent CR.

2. Patients and methods

2.1. Patient selection and data acquisition

Fourteen expert centres were initially invited to participate in this retrospective study, of which 8 centres from 4 European countries (Switzerland, Germany, Italy and France) responded to the invitation. Clinical data of advanced melanoma patients treated with anti-PD1 or anti-PD1/anti-CTLA4 between January 2014 and December 2019 were retrospectively reviewed from institutional databases. Patients who discontinued treatment either electively due to confirmed radiographic or pathologic CR (group A) or due to a TLT or ID (group B) with subsequent CR in both scenarios included in the study. Patients with concurrent experimental therapy (e.g. in terms of a clinical trial) and uveal melanoma were excluded. Complete response (CR) was defined as absence of radiographically apparent disease, defined as inactive disease on FDG-PET/CT scan or as fulfilling CR criteria as per RECIST v1.1. on CT/MRI

scan (radiographic CR), and/or biopsy without evidence of active disease in radiographically apparent residual tissue (pathologic CR). Patients with complete metabolic response on the FDG-PET/CT but with partial response on CT/MRI scan were included. Reason for treatment discontinuation was defined as the decision to stop immunotherapy due to CR (elective discontinuation) or in accordance with patient's and investigator's decision, or due to a TLT. Patients were followed up for at least 6 months from treatment discontinuation or until disease progression or death or December 2019 (cutoff date of the analysis). Co-primary end-points were off-treatment survival (OTS) and PFS, whereas OS was the secondary end-point. A subgroup analysis investigating the intracranial efficacy of these agents in patients with melanoma brain metastasis (MBM) was performed.

2.2. Statistical analysis

Descriptive statistics are presented as percentages of total for categorical variables and as median for continuous and ordinal variables. OS was defined as the time (months) from treatment initiation to death, with censoring on the last known alive date and was estimated with the Kaplan–Meier survival curves. OTS was defined as the median time from last immunotherapy dose to disease progression and PFS was calculated from treatment initiation to disease progression. Off-treatment response time (OTRt) was calculated as the time between last immunotherapy dose to disease progression or last follow-up. A P-value of less than 0.05 was considered statistically significant. All analyses were conducted using statistical language R version 3.5 (R Foundation, USA).

2.3. Ethics statement

The analysis of the registry data was approved by the local ethics committee (KEK-ZH 2014-0193).

3. Results

3.1. Patient characteristics

A total of 125 eligible patients with advanced melanoma were identified. Anti-PD1 monotherapy (pembrolizumab or nivolumab) was administered in 77% (N = 97) of patients, whereas 22.4% (N = 28) of the patients were treated with combination anti-CTLA4/anti-PD1 (ipilimumab/nivolumab or ipilimumab/pembrolizumab). Patients' characteristics are summarized in Table 1. Median follow-up (mFU) was 38 months (range 9–70). Twenty-three patients (18.6%) were previously pretreated with adjuvant agents consisting mostly of interferon-alpha (N = 11) or ipilimumab (N = 1). In the non-resectable stage IV setting, anti-

Table 1
Patient's and disease characteristics.

Characteristic	Stop due to CR	Stop due to TLT or ID
N	**86**	**39**
Age at start of treatment *(mean, range)*	65 (31–89)	70 (21–99)
Male gender (%)	51 (59.3)	31 (79.5)
Mutational status (%)		
BRAF V600 mutant	30 (34.9)	16 (41)
NRAS mutant	19 (22.1)	7 (17.9)
BRAF wt	34 (39.5)	16 (41)
LDH elevated (%)	16 (18.6)	10 (25.6)
Melanoma type (%)		
Cutaneous	72 (83.7)	28 (71.8)
Mucosal	1 (1.2)	1 (2.6)
Unknown primary	9 (10.5)	7 (17.9)
Ulceration (%)	26 (30.2)	12 (30.8)
Previous treatment lines (metastatic setting, %)		
0	36 (41.9)	31 (79.5)
1–2	45 (52.3)	6 (15.4)
≥3	5 (5.8)	2 (5.1)
Previous treatments (metastatic setting, %)		
One prior treatment line		
Immunotherapy	18 (20.9)	1 (2.6)
Targeted therapy	9 (10.5)	0
Multiple prior treatment lines		
Immunotherapy	11 (12.8)	1 (2.6)
Targeted therapy	2 (2.3)	2 (5.1)
Both	6 (7)	2 (5.1)
Disease stage, AJCC 8th (%)		
III	7 (8.1)	7 (17.9)
IV	79 (92)	32 (82)
M stage (%)		
M1a	16 (18.6)	2 (5.1)
M1b	26 (30.2)	6 (15.4)
M1c	23 (26.7)	13 (33.3)
M1d	14 (16.3)	11 (28.2)
Immunotherapy received (%)		
Ipilimumab and nivolumab	6 (7)	19 (48.7)
Ipilimumab and pembrolizumab	2 (2.3)	1 (2.6)
Nivolumab	16 (18.6)	8 (20.5)
Pembrolizumab	62 (72)	11 (28.2)
Brain metastases (MBM) (%)	14 (16.3)	11 (28.2)
RECIST at 3 months after EOT (%)		
CR	82 (95.3)	27 (69.2)
PR	0	10 (25.6)
SD	0	1 (2.8)
Unknown/NA	4 (4.7)	1 (2.8)
RECIST at 6 months after EOT (%)		
CR	74 (86)	31 (86.1)
PD	1 (1.2)	0
PR	0	5 (13.9)
SD	0	1 (2.8)
Unknown/NA	11 (12.8)	2 (5.6)
RECIST at 12 months after EOT (%)		
CR	56 (65.1)	26 (72.2)
PD	2 (2.3)	0
PR	0	2 (5.6)
SD	0	1 (2.8)
Unknown/NA	28 (32.6)	10 (27.8)
RECIST at > 12 months after EOT (%)		
CR	48 (55.8)	24 (66.7)
PD	2 (2.3)	2 (5.6)

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Stop due to CR	Stop due to TLT or ID
Unknown/NA	36 (41.8)	13 (36.1)
Treatment outcome (months)		
DoT *(median, range)*	22 (5–49)	3 (0–36)
Time to CR *(median, range)*	9 (2–47)	7 (1–32)
DoR *(median, range)*	28 (10–56)	24 (0–65)
OTRt *(median, range)*	19 (0–42)	25 (0–66)

CR, complete response; TLT, treatment-limiting toxicity; ID, investigators' decision; DoT, Duration of Treatment, time from treatment initiation to End of Treatment (EOT); Time to CR: time to complete response, time from treatment initiation to first CR; DoR, Duration of Response, time from documentation of tumour response to disease progression; OTRt, off-treatment response time, time from End of Treatment (EOT) until disease progression or death; PR, partial response; SD, stable disease.

PD1-based immunotherapy was administered as first-line treatment in 67 (54%) patients. Excluding the current anti-PD1-based treatment, patients were previously treated with one (N = 32, 26%) or two (N = 19, 15%) to a maximum of four (N = 2, 1.6%) treatment lines and pretreatment consisted mostly of ipilimumab (N = 37, 29.6%). At the time of anti-PD1 treatment initiation, 111 (88.8%) patients had stage IV disease in accordance with AJCC 8th edition. Involvement of two or more organs was present in 68 (54%) patients and 25 (20%) patients had MBM. Serum lactate dehydrogenase (LDH) was elevated in 26 (22%) patients of the study population. Forty-six (38%) patients were *BRAF* mutated.

3.2. Disease control and treatment discontinuation

Of the 125 patients who achieved CR, median duration of treatment (mDoT) was 16 months (range 0–49) and median time to CR was 8 months (range 1–47) since start of immunotherapy (Fig. 1).

3.2.1. Treatment discontinuation due to CR (group A)

Eighty-six patients (68.8%) were considered histologically or radiologically CR and electively discontinued the treatment in the absence of TLT (group A). Median DoT was 22 months (range 5–49) and mDoT after the 1st documentation of CR was 8 months (range 0–40). Median time to CR was 9 months (range 2–47).

3.2.2. Treatment discontinuation due to TLT or ID (group B)

Thirty-nine (31.2%) patients electively discontinued the treatment either due to TLT (N = 33) or due to ID (N = 6), with subsequent CR (group B). Accordingly, mDoT for this group was 3 months (range 0–36) and median time to CR was 7 months (range 1–32). Most patients who discontinued the treatment due to an immune-related adverse event (irAE) had received

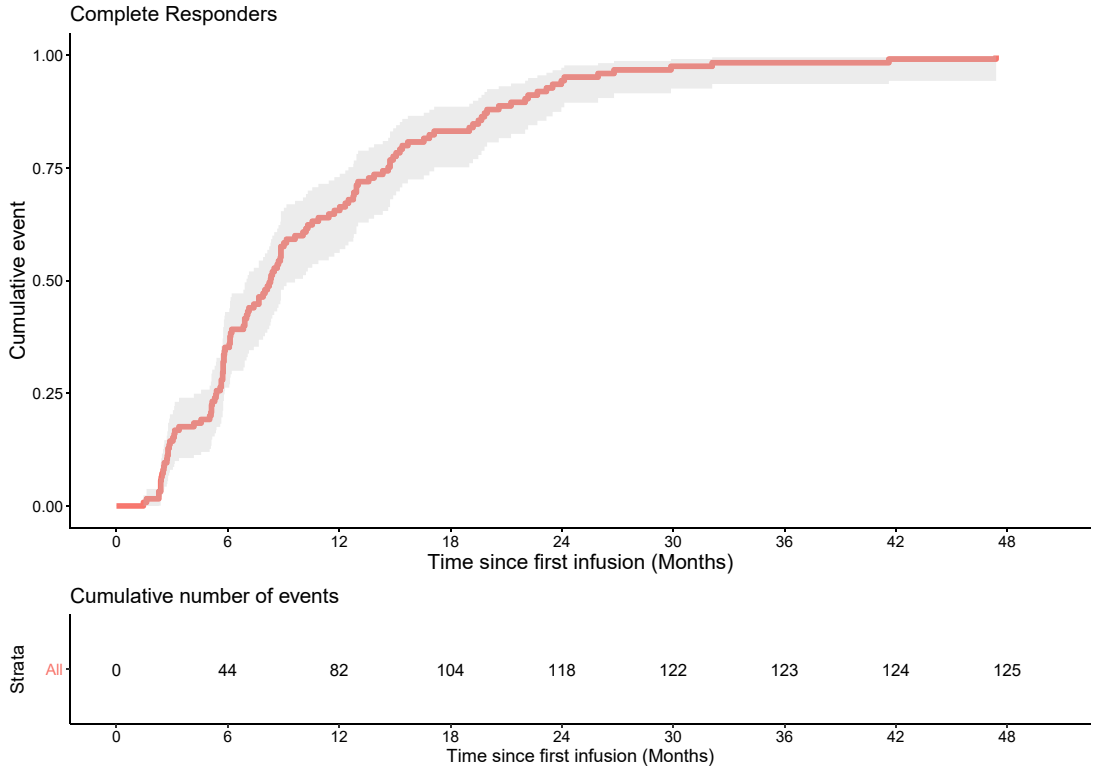


Fig. 1. Incidence of CR as per treatment time for the patient population. Median time to CR was 8 months (range: 1–47 months). CR, complete response.

combined immunotherapy (n = 19 (57.6%)). Frequent irAEs leading to treatment discontinuation (≥grade 3, CTCAE v4) included gastrointestinal (N = 8), endocrinological (N = 6), pulmonary (N = 5), hepatic (N = 4), cutaneous (N = 3), musculoskeletal (N = 2) and neurological (N = 2) toxicities.

3.3. Off-treatment survival, off-treatment response time, subsequent treatment and disease outcome

In total, ten patients (8%) (N = 7 group A and N = 3 group B) ultimately experienced disease recurrence (Figs. 2 and 3).

3.3.1. Treatment discontinuation due to CR (group A)

In group A, two patients who experienced disease recurrence (1.6%) had been treated with combined anti-CTLA4/anti-PD1 and five (4%) with anti-PD1 alone. Subsequent treatments included re-challenge either with anti-PD1 alone (N = 3) or combined immunotherapy (N = 1), or locoregional salvage treatment consisting of wide local excision (N = 1) and radiotherapy (N = 1). One patient with previously known MBM had intracranial PD with extracranial ongoing CR and was treated with neurosurgery and anti-PD1 re-challenge. Of the seven patients who relapsed, one patient (N = 1) developed *de novo* MBM and subsequently underwent stereotactic radiotherapy (SRS) and anti-PD1 re-challenge. Six patients (4.8%) were progression free at data cutoff after subsequent therapy, whereas one patient, in whom no treatment was initiated after disease recurrence, died due to melanoma progression. OTS was not reached. The estimated median OTRt after treatment discontinuation in this group was 19 months (range 0–42) and DoR after declaration of CR was 28 months (range 10–56).

3.3.2. Treatment discontinuation due to TLT or ID (group B)

Three (2.4%) patients, previously treated with combined anti-CTLA4/anti-PD1 (N = 1) and anti-PD1 alone (N = 2) experienced disease relapse in this patient group (group B). Two of three patients had known MBM; one patient (N = 1) experienced intracranial relapse with extracranial ongoing CR and was subsequently treated with neurosurgery and anti-PD1 re-challenge, whereas one patient (N = 1) had extracranial recurrence with intracranial ongoing CR and underwent wide local excision, without systemic treatment. *De novo* MBM was diagnosed in one patient (N = 1) and was subsequently treated with SRS, without systemic treatment initiation. All three patients were free-of progression at data cutoff after the subsequent treatment, with estimated median OTRt at 25 months (range 0–66) and DoR at 24 months (0–65). OTS was not reached.

For group A and B, the estimated median OTRt was 21 months (range 0–66) and DoR after declaration of CR was 37 months (range 9–70). Despite the numerical difference between the two groups, no statistical significant difference in median OTRt was noted (28 and 24 months, respectively) (Table 1 and Fig. 4). In addition, duration of CR was independent of the time to achieve

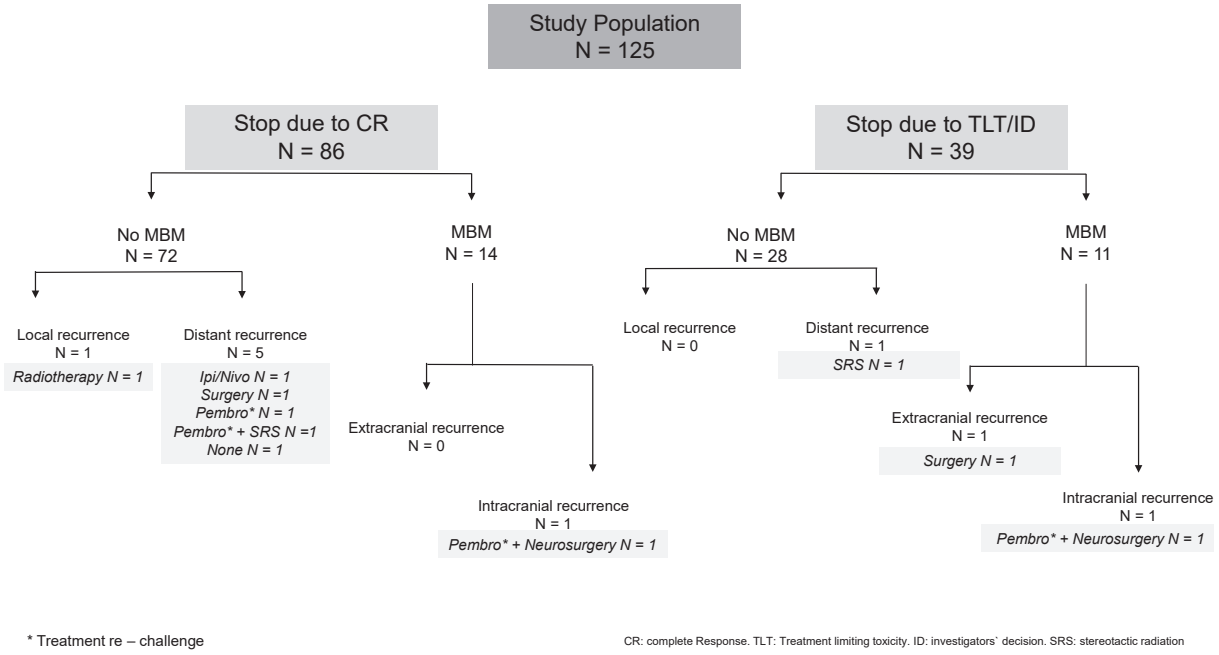
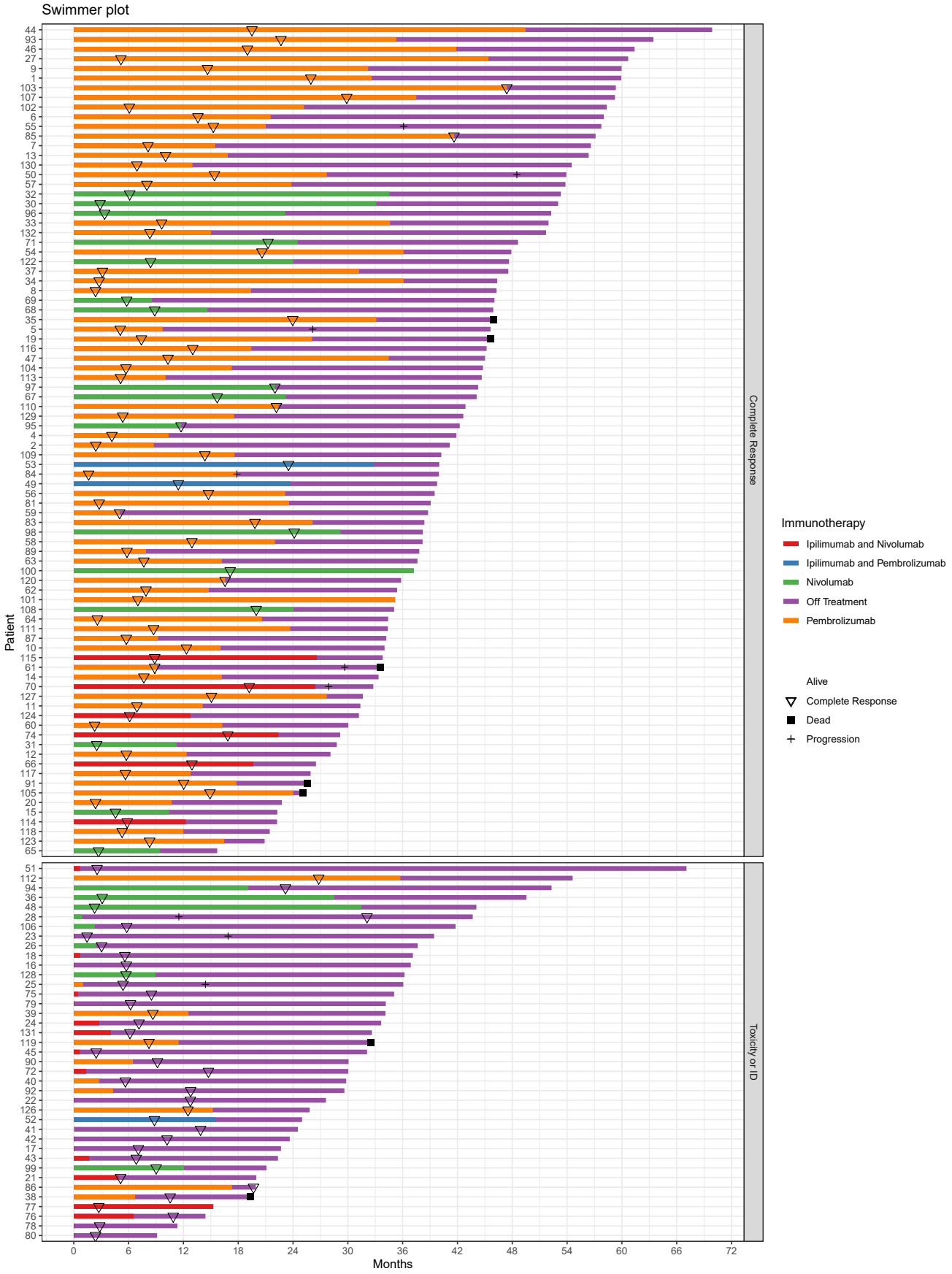


Fig. 2. Study population and disease recurrence characteristics as per reason of treatment discontinuation and the presence of MBM. Of 125 patients treated with anti-PD1–based immunotherapy, ten patients (N = 10) experienced disease recurrence. MBM, melanoma brain metastases.


Swimmer plot
Patient
Months
Complete Response
Toxicity or ID
Immunotherapy
Ipilimumab and Nivolumab
Ipilimumab and Pembrolizumab
Nivolumab
Off Treatment
Pembrolizumab
Alive
Complete Response
Dead
Progression

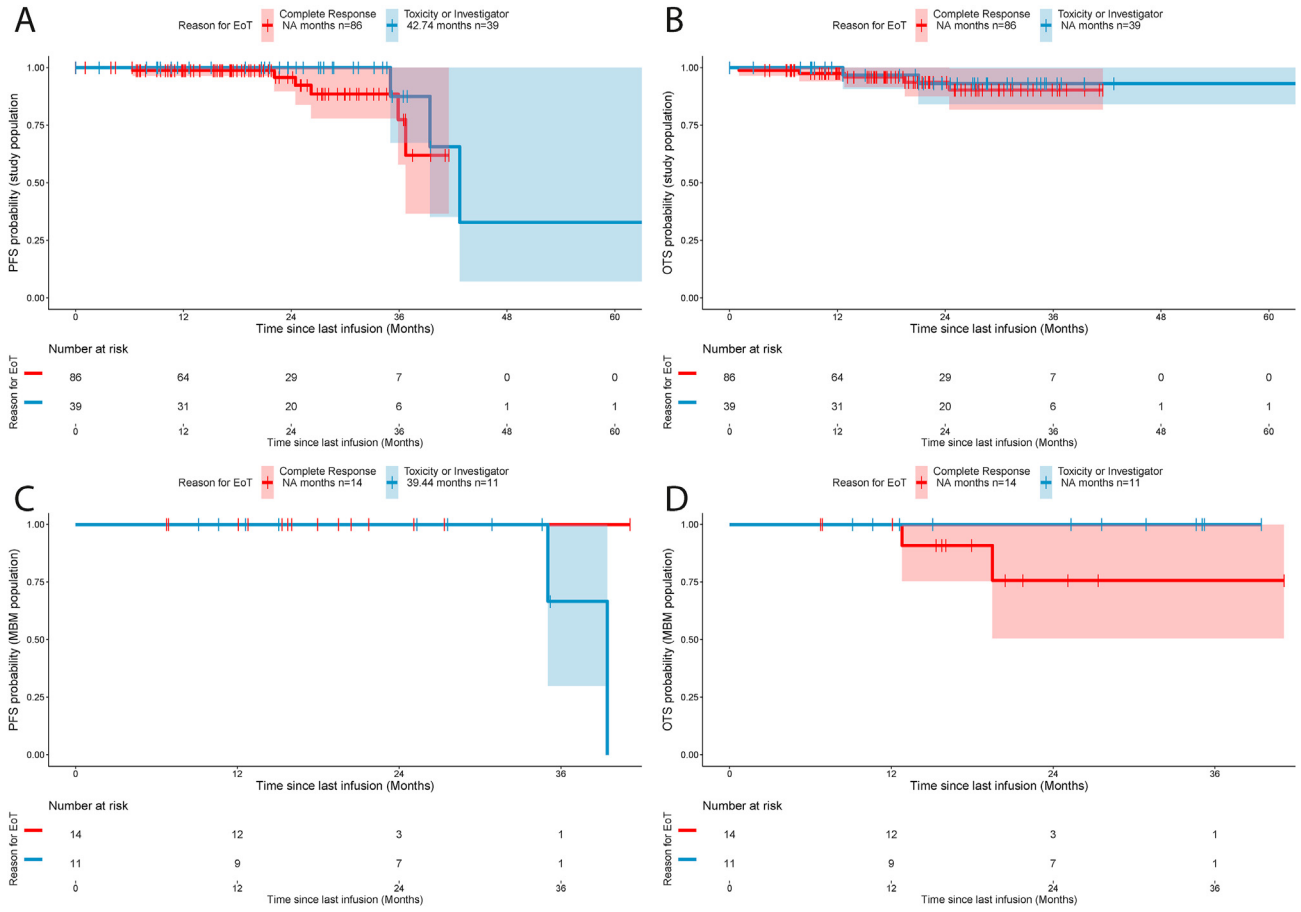


Fig. 4. Kaplan–Meier probability curves for OTS and PFS from treatment discontinuation. PFS (A) and OTS (B) for the study population. A separate analysis was performed for MBM, calculating the PFS (C) and OTS (D) probability, respectively. OTS, off-treatment survival; PFS, progression-free survival; MBM, melanoma brain metastases.

CR in the different subgroups (Fig. 5). By December 31st, 2019, seven (5.6%) patients of the patient cohort had deceased, although only one (0.8%) due to melanoma. Causes of death for the rest of the patients were reported as advanced age (N = 2), cardiac decompensation (N = 1), sepsis due to bacterial lung infection (N = 2) and unknown (N = 1, other than disease progression). Median OS was not reached, 3-year OS was estimated at 90%.

3.3.3. *Melanoma brain metastases*

Twenty-five (20%) patients with MBM treated with anti-PD1/anti-CTLA4 (N = 9) or anti-PD1 alone (N = 16) were subsequently analysed as per DoR and OTRt. MBM patients' characteristics are summarized in Table 2. Apart from systemic treatment, 20 patients (80%) required a local treatment either with SRS (N = 16) or with neurosurgery followed by SRS (N = 4). At the time of immunotherapy initiation, seven (28%) patients were on steroids and nine (36%) patients had elevated LDH. Eleven (44%) patients were *BRAF* mutated and fifteen patients (60%) were treatment naïve for the metastatic setting. Intracranial response at first extracranial CR was achieved in 19 (76%) patients, of which 15 (60%) patients had a CR, three (N = 3) treated with anti-PD1/anti-CTLA4, and twelve (N = 12) with anti-PD1 alone.

Fourteen (N = 14, 56%) patients electively discontinued the systemic treatment due to extracranial and intracranial CR and eleven (N = 11, 44%) due to TLT (N = 10) or ID (N = 1), with subsequent CR (Fig. 6). Median time to CR was 12 months (range 2–30) for the CR group and 5 months (range 1–13) for the TLT/ID group. Median DoR was 29 months (range 12–56) and 27 months (range 7–42) for the two groups, respectively. Median OTRt was calculated at 17 months (range 7–41) for the CR group and 28 months (range 9–39) for the TLT/ID group (Fig. 4). At the end of the observation period, twenty-two (88%) patients remained free of disease and three (N = 3) patients relapsed with extracranial (N = 1) or intracranial (N = 2) relapse. Systemic treatment with anti-PD1–based immunotherapy combined with neurosurgery was initiated in

Fig. 3. Swimmer plots showing the time to CR and durability of response from treatment start to the date of last observation or death, as of December 2019, as per reason for treatment discontinuation. CR, complete response.

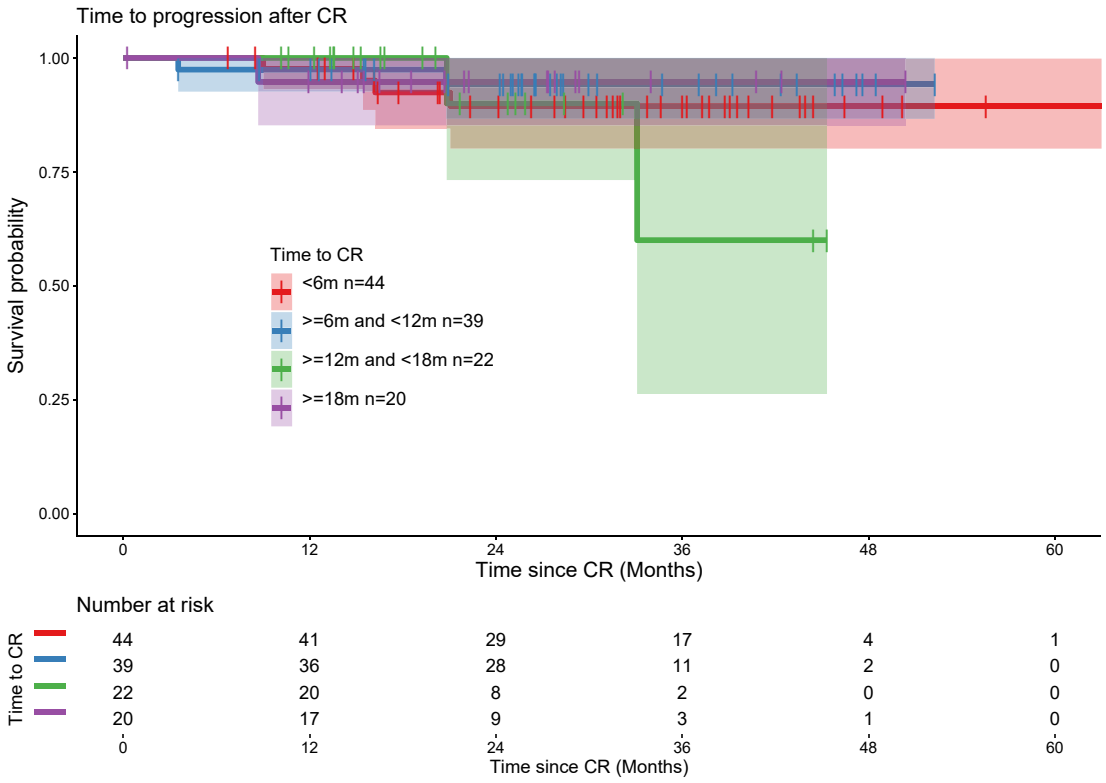


Fig. 5. Kaplan–Meier probability curves for time to progression after achieving CR, compared with the time to CR for <6 months, ≥ 6 months and <12 months, ≥12 months and <18 months and ≥18 months. CR, complete response.

both patients with intracranial relapse, whereas extracranial relapse was treated with wide local excision. All patients showed benefit form retreatment. As of December 2019, 23 patients were still alive and 2 had deceased due to reduced performance status, without evidence of PD.

4. Discussion

In this multicenter study of patients with advanced melanoma who electively discontinued anti-PD1–based immunotherapy due to CR, we observed sustained responses, suggesting that treatment discontinuation is feasible also in patients with MBM. Although the discontinuation criteria were not homogeneous for the treatment population, the probability of being alive without additional therapy at 3 years was 92%. In patients who experienced disease relapse after treatment discontinuation, re-challenge with anti-PD1–based ICI was mostly preferred from the investigators with renewed response. Likewise, durable responses after early treatment cessation were reported in patients with melanoma who had achieved CR in the KEYNOTE-001 study, with 91% remaining free of disease after a minimum of 5 years follow-up [8]. Re-treatment with anti-PD1 could be effective, as similarly reported in the KEYNOTE-006 study [4] and in a recent, retrospective analysis [10].

Notably, sustained disease control was observed in 115 patients who discontinued the systemic treatment due to TLT or ID. Compared with the patients with treatment discontinuation due to CR, mDoT in this patient group was significantly shorter (3 months and 22 months, respectively), indicating that most patients who discontinued due to an irAE did so early after the ICI initiation. Still, median time to CR (7 and 8 months, respectively), as well as efficacy outcomes seemed to be similar in both groups with no difference in median OTRt. These data are in line with previously reports investigating the safety and efficacy in patients treated with ipilimumab and nivolumab who discontinued due to an irAE [11], suggesting that irAEs provide evidence that an immune reaction has been activated. Whether this activation correlates with an increased antitumour activity and thus, favourable prognosis remains unclear [12].

Patients with MBM have a dismal prognosis and until recently they were typically excluded from clinical trials. Two randomized, phase 2 clinical trials showed that anti-PD1–based ICIs and especially combined immunotherapy with ipilimumab/nivolumab are intracranially active [13,14]. In our pooled population, 20% of the patients had active MBM during the treatment initiation and at the time of treatment discontinuation, the vast majority of the patients had concordant extracranial and intracranial efficacy. Still, 84% of the

Table 2
Melanoma brain metastases (MBM) patients' characteristics.

	Stop due to CR	Stop due to TLT or ID
N	**14**	**11**
Male gender (%)	10 (71.4))	9 (81.8)
Age at start of treatment *(mean, range)*	66 (31–89)	73 (39–82)
Mutational status (%)		
BRAF V600 mutant	3 (21.4)	8 (72.7)
NRAS mutant	6 (42.9)	0
BRAF wt	5 (35.7)	3 (27.3)
Elevated baseline LDH	3 (21.4)	6 (54.5)
Previous treatment lines (metastatic setting, %)		
0	7 (50)	8 (72.7)
1–2	6 (42.9)	1 (18.2)
≥ 3	1 (7.1)	2 (18.2)
Immunotherapy received (%)		
Ipilimumab and nivolumab	2 (14.3)	6 (54.5)
Ipilimumab and pembrolizumab	1 (7.1)	0
Nivolumab	0	2 (18.2)
Pembrolizumab	11 (78.6)	3 (27.3)
Treatment of MBM (%)		
SRS	8 (57.1)	8 (72.7)
SRS + OP	4 (28.6)	0
None	2 (14.3)	3 (27.3)
Steroids needed (%)		
Yes	4 (28.6)	3 (27.3)
Intracranial response at EOT (%)		
CR	11 (78.6)	4 (36.4)
PR	0	4 (36.4)
SD	3 (21.4)	2 (18.2)
Treatment outcome (months)		
DoT *(median, range)*	23 (11–49)	2 (0–31)
Time to CR *(median, range)*	12 (2–30)	5 (1–13)
DoR *(median, range)*	29 (12–56)	27 (7–42)
OTRtS *(median, range)*	17 (7–41)	28 (9–39)

CR, complete response; TLT, treatment-limiting toxicity; ID, investigators' decision; DoT, Duration of Treatment, time from treatment initiation to End of Treatment (EOT); Time to CR, time to complete response, time from treatment initiation to first CR; DoR, Duration of Response, time from documentation of tumour response to disease progression; OTRt, off-treatment response time, time from End of Treatment (EOT) until disease progression or death; PR, partial response; SD, stable disease; SRS, stereotactic radiation; OP, operation (neurosurgery).

patients received a local treatment, consisting mostly of SRS, suggesting that in real-life, local management is still preferred from investigators, regardless of concurrent systemic treatment initiation and the possible increased risk of radionecrosis [15]. Median time to CR was according to patients without MBM, regardless of reason for treatment cessation. Similarly, although mDoT differed between group A and B patients, median OTRt was similar. In patients who progressed, no patterns of progression could be identified, but not all patients who progressed had an intracranial progression. However, the numbers are too small to draw any conclusions.

Despite a principal approval for a long-term use, the optimal treatment duration of ICI is still a matter of debate. In clinical trials, anti-PD1 antibodies are typically administered continuously over 2 years, or until reaching a TLT or PD. In the KEYNOTE-001 study treatment cessation was allowed for patients achieving CR and ≥6 months of treatment and at least 2 treatments after CR confirmation [8]. In our study, mDoT for the patients who electively discontinued due to CR was 22 months and mDoT after CR 8 months. Recent data identified a significantly increased risk of subsequent relapse in patients treated with anti-PD-1 treatment for <6 months versus >6 months [10]. Although previous reports indicate that prolonged treatment does not result in an increased incidence of AEs [16], the incidence of long-term toxicities is still unknown [17]. To date, there are still no definite predictors for treatment response and indicators for cessation decisions. Recent *post hoc* results from the KEYNOTE-001 clinical trial have provided evidence that tumour size and PD-L1 status at the baseline were associated with CR by univariate analysis [9]. Despite recent findings supporting that metabolic CR on FDG-PET scans is likely to influence the treatment duration decision [18], two retrospective studies of real-life patients achieving CR and discontinuing treatment in absence of TLT reported that a significant number of patients showed persisting radiological evidence of disease [10,19]. Previously published studies have linked lower frequency of *BRAF V600 mutation* and elevated LDH, as well as lower tumour stage and incidence of MBM with better clinical outcome [10].

The retrospective nature of the data, the patients' selection (only complete responders) and the lack of an established consensus for treatment discontinuation, as well as the lack of central radiologic review are possible limitations of this analysis. In real life, significant amount of ICI-treated patients achieve a PR as best overall response, in accordance with the RECIST 1.1 criteria. In this study, patients with PR on the CT/MRI scan but CR on the FDG-PET/CT were included. ICI cessation of partial responders either electively or due to TLT with subsequent PR was not the focus of the present study. However, it remains one of the major challenges for physicians, as they are often confronted by a patient's will to continue ICI despite notable toxicity in some cases, remarkable treatment-related costs and the fact that risk of subsequent relapses is higher in patients achieving PR than in those with CR.

Although treatment discontinuation after achieving CR seems feasible, the discontinuation criteria for stopping treatment merit additional investigation. Despite the relatively small number of re-treatments after disease relapse, our cohort indicates that re-treatment is feasible and may lead to renewed anti-tumour activity in patients after treatment discontinuation. Randomized, prospective studies are recommended to evaluate an optimal and pragmatic treatment duration to prevent over- and under-

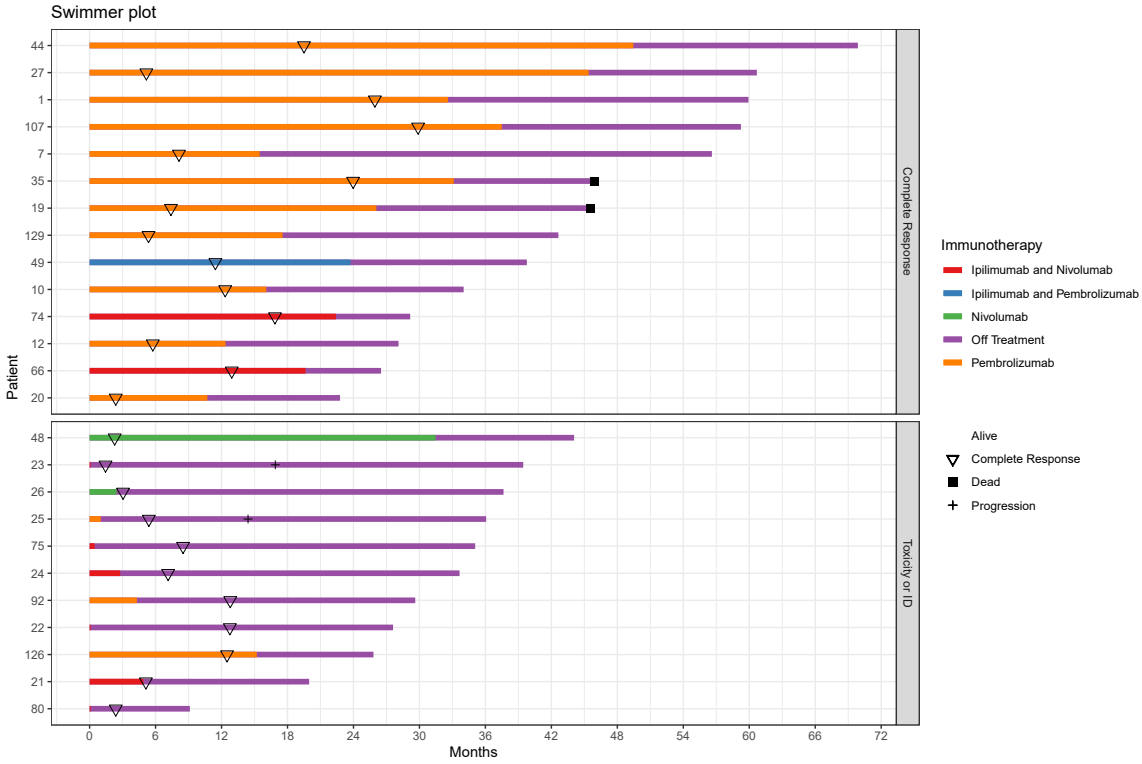


Fig. 6. Swimmer plots showing the treatment course for patients with MBM. Time to CR and durability of response from treatment start to the date of last observation or death, according to reason for treatment discontinuation. Data cutoff in December 2019. MBM, melanoma brain metastases; CR, complete response.

treatment, long-term toxicities and financial costs from overtreatment.

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Authors' contributions

Study design and study concepts were contributed by FD, ER, JM and RD. Data acquisition was carried out by FD, ER, AZ, CA, KCK, CLG, LF, SS, FT, LH and JM. Quality control of data and algorithms was contributed by FD and JM. Data analysis and interpretation was contributed by FD, PFC, JM and RD. Statistical analysis was done by FD, ER and PFC. Manuscript preparation was carried out by FD. Manuscript editing was contributed by FD and JM. Manuscript review was performed by FD, AZ, CA, KCK, CLG, LF, SS, FT, LH, JCH, PAA, OM, AH, CL, EL, ER, PFC, JM and RD.

Conflict of interest statement

FD receives intermittent travel support from Pierre Fabre outside of the submitted work.

AZ has received travel grants from Novartis and BMS outside of the submitted work.

AC receives meeting, accommodation and travel support from Roche, Amgen and BMS.

KCK serves as consultant to Roche, BMS, MSD and received travel grants and speaker fees from Roche, BMS, MSD, GSK, Amgen.

LF reports grants from Novartis, grants from BMS, grants from MSD, outside the submitted work; FT received travel support from Novartis and Abbvie.

LH receives fees for consultant/advisory role: Amgen, Bristol-Myers Squibb, Curevac, Roche Pharma, MSD Sharp & Dohme Sharp & Dohme, Novartis, Sanofi, Pierre Fabre. Research funding: Novartis.

JH has intermittent project focused consultant or advisory relationships with Merck Sharp & Dohme, Pierre Fabre and Sunpharma and has received speaker honoraria from Novartis, BMS and travel support from Pierre Fabre and BMS outside of the submitted work.

PAA has/had a consultant/advisory role for Bristol Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, AstraZeneca, Syndax, SunPharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar, Boehringer-Ingelheim. He also received research funds from Bristol Myers Squibb, Roche-Genentech, Array and travel support from MSD.

OM reports grants and personal fees from Bristol Myers Squibb (BMS), grants and personal fees from MSD, personal fees from Roche, outside the submitted work.

AH received consultancy and speaker honoraria from the following companies: Amgen, BMS, MerckPfizer, MSD, Novartis, Philogen, Pierre Fabre, Provectus, Regeneron and Roche.

CL received consultancy and speaker honoraria from the following companies: Amgen, BMS, MerckPfizer, MSD, Novartis, Pierre Fabre and Roche.

EL served as consultant or/and has received honoraria from Amgen, Actelion, Roche, Bristol Myers Squibb (BMS), Merck Sharp & Dohme (MSD, Novartis, Janssen, Medac and travel support from Amgen, Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Amgen, Pierre Fabre, Sunpharma and Novartis.

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CG, SSch and PFC have declared no conflicts of interest.

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